Genetic heterogeneity in infantile spasms

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ABSTRACT

Infantile spasms (IS) is a developmental and epileptic encephalopathy with heterogeneous etiologies including many genetic causes. Genetic studies have identified pathogenic variants in over 30 genes as causes of IS. Many of these genetic causes are extremely rare, with only one reported incidence in an individual with IS. To better understand the genetic landscape of IS, we used targeted sequencing to screen 42 candidate IS genes and 53 established developmental and epileptic encephalopathy genes in 92 individual with IS. We identified a genetic diagnosis for 7.6% of our cohort, including pathogenic variants in *KCNB1* (n = 2), *GNAO1* (n = 1), *STXBP1* (n = 1), *SLC35A2* (n = 1), *TBL1XR1* (n = 1), and *KIF1A* (n = 1). Our data emphasize the genetic heterogeneity of IS and will inform the diagnosis and management of individuals with this devastating disorder.

1. Introduction

Infantile spasms (IS) are a relatively common type of epileptic seizure, usually beginning in the early infantile period and characterized by clusters of flexion or extension limb and trunk spasms. These spasms are often accompanied by the electroencephalography (EEG) pattern of hypsarrhythmia. Despite advances in the early diagnosis and treatment of IS, the neurodevelopmental outcome for patients remains poor. IS frequently leads to developmental arrest or regression, intellectual disabilities, and/or chronic refractory seizures (Pellock et al., 2010).

The etiology of IS is highly heterogeneous, in part because IS can be the clinical expression of a variety of genetic or acquired conditions.

Abbreviations: AC, allele count; ACMG, American College of Medical Genetics and Genomics; DEE, developmental and epileptic encephalopathy; EEG, electroencephalography; IS, Infantile spasms; MIPs, molecular inversion probes; NLES, non-lesional epileptic spasms; smMIPs, single molecule molecular inversion probes

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Table 1
Pathogenic variants and variants of unknown significance (VOUS) identified in this study.

Gene	Inheritance	Inferred Effect	GRCh37/hg19 Genomic Coordinate	cDNA Change	Protein Change	CADD	gnomAD(AC)
GNAO1	*de novo*	Likely-pathogenic	chr16:g.56368706 G > C	NM_138736.2:c.530 G > C	p.(Arg177Pro)	35.0	0
KCNB1	*de novo*	Pathogenic	chr20:g.47990350 G > A	NM_004975.2:c.1747C > T	p.(Arg583*)^	37.0	0
KCNB1	*de novo*	Pathogenic	chr20:g.47990988C > T	NM_004975.2:c.1109 G > A	p.(Trp370*)	39.0	0
SLC35A2	*de novo*	Likely-pathogenic	chrX:g.48763706 T > C	NM_005660.1:c.389A > G	p.(Tyr130Cys)	22.9	0
STXBP1	*de novo*	Likely-pathogenic	chr9:g.130416028 T > C	NM_003165.3:c.122 T > C	p.(Leu41Pro)	24.1	0
TBL1XR1	*de novo*	Likely-pathogenic	chr3:g.176771679C > T	NM_024665.4:c.86 G > A	p.(Gly29Asp)	33.0	0
KIF1A	unknown	Pathogenic	chr2:g.241723197C > T	NM_001244008.1:c.757 G > A	p.(Glu253Lys)^	34.0	0
	19.7% Mosaic	VOUS	chr2:g.241662963C > T	NM_001244008.1:c.4331 G > A	p.(Arg1444Gln)	35.0	1
FASN	*de novo*	VOUS	chr17:g.80044266 G > A	NM_004104.4:c.3596C > T	p.(Ala1199Val)	6.06	3
HDAC4	unknown	VOUS	chr2:g.239990214 G > A	NM_006037.3:c.2825C > T	p.(Pro942Leu)	20.4	0
PNMAL1	unknown	VOUS	chr19:g.46973812 T > C	NM_018215.3:c.481A > G	p.(Ile161Val)	9.21	0
PPP3CA	unknown	VOUS	chr4:g.102015013 G > T	NM_000944.4:c.702C > A	p.(Asp234Glu)	27.0	0

^, recurrent pathogenic variant.

Major causes of IS include extrinsic brain injuries, metabolic encephalopathies, brain malformations, and chromosomal abnormalities; however, approximately 30% of cases remain unexplained (Pellock et al., 2010). Genetic studies of individuals with unexplained IS have identified pathogenic variants in over 30 genes (McTague et al., 2016), many of which are also associated with other seizure types. Variants in these genes only account for 11–29% of unsolved IS cases (Boutry-Kryza et al., 2015; Epi et al., 2013; Michaud et al., 2014), suggesting that many IS genes have yet to be identified.

We performed targeted massively parallel sequencing of 42 candidate IS genes and 53 established developmental and epileptic encephalopathy (DEE) genes in 92 individuals with IS. We identified pathogenic variants in 7.6% of our cohort. *KCNB1* was the only gene where pathogenic variants were found in more than one individual.

2. Methods

2.1. Cohort

Individuals recruited through the EuroEPINOMICS-RES consortium for the project on non-lesional epileptic spasms (NLES) were enrolled by 10 clinical sites in 9 different European countries. Inclusion criteria included documented infantile spasms with onset in the first 2 years of life, normal routine metabolic screening, and absence of epileptogenic lesion on brain MRI. Most individuals had undergone testing for known genetic causes of infantile spasms, but this was not required for study inclusion. Individuals with a family history of epilepsy in first-degree relatives were excluded. Genomic DNA of the individuals was extracted from peripheral blood according to standard procedures. The study was approved by the local ethics committee of each participating center. Parents or the legal guardian of each study participant signed an informed consent form for participation.

2.2. Gene selection for targeted sequencing

We selected 95 genes for sequence analysis: 39 genes in which at least one individual with IS was reported to have a *de novo* variant in another study (Conti et al., 2015; Endele et al., 2010; Epi et al., 2013; Euro et al., 2014; Helbig et al., 2018; Ishii et al., 2017; Langlois et al., 2016; Michaud et al., 2014; Saitsu et al., 2014); three candidate IS genes located in pathogenic copy number variants; and 53 established DEE genes to ensure uniform testing across the cohort. A complete list of genes sequenced in this study can be found in **Supplementary Table 1.**

2.3. Targeted sequencing of candidate genes

Molecular inversion probes (MIPs) or single molecule MIPs (smMIPs) were use to target all coding exons and intron/exon boundaries (5 flanking base pairs) of each of the 95 target genes. Library preparation, sequencing, and processing were performed as previously described (Myers et al., 2017). A read-depth of 50X (MIPs) or 8X (smMIPs) and an allele balance of greater than 25% (MIPS) or 15% (smMIPs) were required for accurate variant calling. Variants not predicted to impact protein coding sequence (synonymous and intronic) and variants present (AC > 3) in genome Aggregation Database (gnomAD v2.1.1), or with an allele frequency > 1% for recessive analysis, were excluded from further analysis.

2.4. Criteria for pathogenicity

Segregation analysis was carried out on all rare protein effecting variants by targeted sequencing. Variants were considered pathogenic or likely-pathogenic according to ACMG guidelines(Richards et al., 2015). In all families with an identified *de novo* mutation, we used microsatellite analysis (PowerPlex S5 system, Promega) or targeted capture (smMIPs) of an in house 51 single nucleotide polymorphism (SNP) marker set to confirm relatedness of the trio. All reported variants were validated by Sanger sequencing.

3. Results

We sequenced candidate or known IS genes in a cohort of 92 individuals with unexplained IS. On average, 84% of the target was covered above the threshold needed for accurate variant calling (Supplementary Table 1). Pathogenic variants were identified in 7 of the 92 individuals (7.6%) (Table 1). These variants were distributed over 6 of the 95 genes screened (*GNAO1, KCNB1, KIF1A, SLC35A2, STXBP1,* and *TBL1XR1*). *KCNB1* was the only gene where pathogenic variants were found in more than one individual (n = 2). Variants of uncertain significance were identified in *FASN*, *HDAC4, PNMAL1*, and *PPP3CA* (Table 1). Detailed phenotyping information for individuals for whom we have identified a causative variant can be found in Table 2.

4. Discussion

This study confirms the genetic heterogeneity of IS. We identified a genetic etiology for 7.6% of individuals in our series, with variants in no single gene accounting for greater than 3% of our cohort. We identified 5 pathogenic variants in 4 established IS genes, *KCNB1*, *GNAO1*, *STXBP1*, and *SLC35A2*. Of the 42 candidate IS genes we screened, we identified pathogenic variants in two genes *TBL1XR1* (MIM: 608628) and *KIF1A* (MIM: 601255).

Transducin β-like 1 X-linked receptor 1 (TBL1XR1) is a co-repressor of nuclear hormone transcription factors and is required for Wnt signaling. Pathogenic *de novo* variants in the C-terminal WD-40 repeats of TBL1XR1 have been identified in individuals with autism (O'Roak et al., 2012) and Pierpont syndrome (Heinen et al., 2016). Saitsu et al.

Table 2
Clinical features of individuals with identified pathogenic variants.

Variant	GNAO1 p.(Arg177Pro)	KCNB1 p.(Arg583*)	KCNB1 p.(Trp370*)	KIF1A p.(Glu253Lys)	SLC35A2 p.(Tyr130Cys)	STXBP1 p.(Leu41Pro)	TBL1XR1 p.(Gly29Asp)
Age (gender)	–	–	4 y (M)	4 y (F)	F (5 y)	–	–
Epilepsy syndrome	WS, LGS	WS	WS	IS	IS	WS	WS
Presenting sz (age)	IS (6 w)	IS (5 m)	IS (4 m)	IS (6 m)	IS (1 m)	IS (4 m)	IS (6 m)
EEG at onset	Suppression- burst	Hypsarrhythmia	Hypsarrhythmia	Multifocal epileptic abnormalities	Multifocal epileptic abnormalities	Hypsarrhythmia	Hypsarrhythmia
Further sz types	Myoclonic	No	–	–	Focal motor	Tonic, absence, myoclonic-astatic, myoclonic	–
EEG at follow-up (age)	Slow background, no epileptiform discharges (8 y, 11 y, 13 y, 14 y)	Normal	Normal (3 y)	Multifocal epileptic abnormalities (4 y)	Fronto-temporal L epileptic abnormalities (5 y)	Monomorphic slow background, multifocal spikes, generalized fast paroxysmal activity in sleep (14 y), slow background, fronto-temporal spikes (16 y)	Normal
Neuroimaging (age)	Normal (3 m)	Normal (5 m, 2 y)	Normal (2 y)	Multiple signal hyperintensities, thin corpus callosum, cerebellar atrophy (3 y)	Enlarged ventricles, large cerebellar cystic dilation (4 y)	Normal (8 y)	Mild delayed myelination; poor white matter development; mild vermis hyoplasia and thin corpus callosum (6 m, 30 m, 5y)
Cognition before sz onset	NA	Normal	Normal	Delayed milestones	Delayed milestones	Normal	Mild DD
Cognition after onset	Severe ID	Severe ID	Stagnation, mild ID	Cognitive regression, severe ID	Stagnation, severe ID	Severe ID	Moderate ID
Behavioral issues	Hyperactivity	No	Autistic Features	No	No	Autism	Hyperactive behavior and attention deficit disorder
Neurological examination	Microcephaly, ataxia, spastic gait, walks a few steps	No speech	–	Microcephaly, hypotonia, absent language, nystagmus	Microcephaly, hypotonia, absent language, nystagmus, strabismus	Spasticity, ataxia, hypotonia	–
Treatment response	Long term sz free on VGB and VPA, no AEDs in the last 9 y	Response to ACTH, no AEDs at present, no further sz	Good response	Poor response	Partial benefit	Response to ACTH, sz free form the age of 7 m to 6 y, later drug-resistant	Response to ACTH, no AEDs at present
Other features	Facial dysmorphia (telecanthus, short philtrum, large ear lobe, low set ears, long thumbs and short Vth finger on hands), scoliosis	R leg hyperchromic skin spot, bilateral hands clinodactyly	–	Dysmorphic features, optic atrophy	–	–	No

Abbreviations are as follows: ACTH, adrenocorticotropic hormone; AEDs, antiepileptic drugs; CBZ, carbamazepine; DD, developmental delay; DTP, diphtheria pertussis tetanus; F, female; hrs, hours; ID, intellectual disability; IS, infantile spasms; L, left; LEV, levetiracetam; LGS, Lennox-Gastaut Syndrome; LTG, lamotrigine; M, male; m, months; NA, not applicable; R, right; Sz, seizure; w, weeks; WS, West Syndrome; VGB, vigabatrin; VPA, valproate; y, years; -, information unavailable.

identified a girl with West syndrome with a *de novo* p.Gly70Asp variant in the N-terminal F-box domain of TBL1XR1 (Saitsu et al., 2014). We have identified a second individual with West syndrome who has a *de novo* p.Gly29Asp variant in the N-terminal LisH domain of TBL1XR1, strengthening the case for *TBL1XR1* as an IS gene.

We also identified a pathogenic variant in kinesin family member 1A (*KIF1A*), which encodes a neuron-specific microtubule-dependent molecular motor protein responsible for transport of synaptic vesicle precursors along axons. Pathogenic *de novo* variants in the motor domain of KIF1A can result in a complex degenerative neurologic phenotype characterized by severe developmental delay, and a variable combination of progressive cerebral and cerebellar atrophy, optic nerve atrophy, progressive spasticity, hypotonia, and peripheral neuropathy (Esmaeeli Nieh et al., 2015; Lee et al., 2015). While approximately one third of individuals with pathogenic heterozygous *KIF1A* variants have epilepsy, only one individual, with a diagnosis of PEHO-like syndrome, has been reported to have IS (Langlois et al., 2016). We identified a heterozygous p.Glu253Lys variant in the motor domain of KIF1A in a girl with severe developmental delay and cognitive regression, cerebellar atrophy, hypotonia, optic atrophy, and refractory IS. While parental DNA was unavailable, the same variants have been reported as pathogenic in three other individuals with complex degenerative neurologic phenotypes (Esmaeeli Nieh et al., 2015; Lee et al., 2015). One previously reported individual with *KIF1A* p.Glu253Lys had no history of seizures, one had unspecified seizures, and one had no information on seizure history available. This coincides with the overall trend of variable expressivity seen in other recurrent *KIF1A* variants (Esmaeeli Nieh et al., 2015; Langlois et al., 2016; Lee et al., 2015). We identified a second *KIF1A* variant in this individual, a somatic mosaic p.Arg1444Gln mutation. This mutation is located outside of the motor domain where all other pathogenic *de novo KIF1A* missense variants are located and is therefore unlikely to have a pathogenic effect on the protein.

The only gene for which we found multiple individuals with *de nov* variants was *KCNB1*, which encodes the Kv2.1 potassium channel (MIM: 600397). Pathogenic *KCNB1 de novo* variants have been reported in several children with neurodevelopmental disorders, 36% of whom had a history of spasms (de Kovel et al., 2017). The majority of *KCNB1* pathogenic variants identified have been missense variants, which tend to cause intractable epilepsy and severe developmental delay. The few protein-truncating variants identified have been in individuals with developmental delay but milder seizure phenotypes (de Kovel et al., 2017). We identified two individuals with *de novo* nonsense mutations in KCNB1, p.Arg583* and p.Trp370*. Both individuals had strikingly similar seizure histories: spasm onset before 6 months of age, seizures controlled by medication, and the development of no additional seizure types.

Previous large cohort genetic studies in IS have identified pathogenic variants in 11–29% of individuals (Boutry-Kryza et al., 2015; Epi et al., 2013; Michaud et al., 2014). With the exception of *CDKL5*, *STXBP1*, and now *KCNB1*, no IS study has identified multiple individuals with *de novo* variants in the same gene. This has hampered the identification of novel IS genes. To increase the likelihood of finding additional cases, we screened genes where a *de novo* variant had already been identified in an individual with IS. We were able to identify additional pathogenic variants in 2 of 42 candidate IS genes. However, it is likely that there are additional cases for many of the other candidate genes. Genetic studies in much larger cohorts or the use of online tools to connect genetics researchers from around the world will be needed to identify additional genetic causes of IS.

Declaration of competing interest

HMC is a member of scientific advisory boards for Lennox Gastaut Syndrome Foundation, Dravet Syndrome Foundation, and SPARK. The remaining authors have no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2019.106181.

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Web Resources

gnomAD v2.1.1: https://gnomad.broadinstitute.org/

CADD: http://cadd.gs.washington.edu/